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CLAIMS

What is claimed is:

1. A recombinant hybrid virus, comprising:

- 5 (a) a deleted adenovirus vector genome comprising the adenovirus 5' and 3' *cis*-elements for viral replication and encapsidation, and further comprising a deletion in an adenovirus genomic region selected from the group consisting of:
- 10 (i) the polymerase region, wherein said deletion essentially prevents the expression of a functional polymerase protein from said deleted region and said hybrid virus does not otherwise express a functional polymerase protein,
- 15 (ii) the preterminal protein region, wherein said deletion essentially prevents the expression of a functional preterminal protein from said deleted region, and said hybrid virus does not otherwise express a functional preterminal protein, and
- 20 (iii) both the regions of (i) and (ii); and
- (b) a recombinant adeno-associated virus (AAV) vector genome flanked by the adenovirus vector genome sequences of (a), said recombinant AAV vector genome comprising (i) AAV 5' and 3' inverted terminal repeats,
- 25 (ii) an AAV packaging sequence, and (iii) a heterologous nucleic acid sequence, wherein said heterologous nucleic acid sequence is flanked by the 5' and 3' AAV inverted terminal repeats of (i).

2. The recombinant hybrid virus of Claim 1, wherein said adenovirus 5' and 3' *cis*-elements comprise 5' and 3' adenovirus inverted terminal repeats and an adenovirus packaging sequence

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3. The recombinant hybrid virus of Claim 1, wherein said AAV inverted terminal repeats are selected from the group consisting of AAV-1, AAV-2, AAV-3, AAV-4, AAV-5 and AAV-6 inverted terminal repeats.

4. The recombinant hybrid virus of Claim 1, wherein said AAV
5 vector genome does not encode the AAV Rep or AAV capsid proteins.

5. The recombinant hybrid virus of Claim 1, wherein said adenovirus vector genome comprises sequences encoding an AAV Rep protein.

6. The recombinant hybrid virus of Claim 5, wherein said
10 sequences encoding said AAV Rep protein are operably associated with an inducible promoter.

7. The recombinant hybrid virus of Claim 6, wherein said inducible promoter is selected from the group consisting of a tetracycline response element, an ecdysone response element, a heat shock promoter, an MMLV long terminal repeat sequence, bacteria phage T7 promoter, a
15 metalothionein response element, and the AAV p5 promoter.

8. The recombinant hybrid virus of Claim 5, wherein said sequences encoding said AAV Rep protein are operably associated with a promoter selected from the group consisting of a liver-specific, muscle-specific, and brain-specific promoter.
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9. The recombinant hybrid virus of Claim 1, wherein said adenovirus vector genome comprises sequences encoding an AAV capsid protein.

10. The recombinant hybrid virus of Claim 1, wherein said
25 adenovirus vector genome comprises sequences encoding the adenovirus helper functions for AAV replication and packaging.

11. The recombinant hybrid virus of Claim 10, wherein said adenovirus vector genome comprises a functional adenovirus genomic region selected from the group consisting of an adenovirus E1a region, E2a region, E4orf6 region, VA RNA region, and any combination of the
30 foregoing.

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12. The recombinant hybrid virus of Claim 1, wherein said adenovirus vector genome further comprises a deletion in an adenovirus E1 region, wherein said deletion essentially prevents the expression of one or more functional E1 proteins from said deleted region.

5 13. The recombinant hybrid virus of Claim 9, wherein said recombinant AAV genome is inserted into the deleted adenovirus E1 region of said adenovirus vector genome.

14. The recombinant hybrid virus of Claim 12, wherein said adenovirus vector genome does not otherwise express a functional E1 gene
10 product.

15. The recombinant hybrid virus of Claim 1, wherein said hybrid virus can complete viral replication in a helper cell that complements the deletions in the adenovirus vector genome.

16. The recombinant hybrid virus of Claim 1, wherein said
15 adenovirus vector genome further comprises a deletion in an adenovirus region selected from the group consisting of the IVa2 region, the 100K region, the E3 region, the E2a region, the E4 region, the L1 region, the L2 region, the L3 region, the L4 region, the L5 region, the intermediate gene IX region, and any combination of the foregoing, wherein said adenovirus
20 vector genome does not otherwise express a gene product associated with the deleted region.

17. The recombinant hybrid virus of Claim 1, wherein said adenovirus vector genome comprises a deletion in the preterminal protein region.

25 18. The recombinant hybrid virus of Claim 17, wherein said deletion comprises a deletion in the preterminal protein region at about nucleotides 9198 to 9630 of the adenovirus serotype 5 genome or a corresponding region of the genome of an adenovirus of another serotype.

19. The recombinant hybrid virus of Claim 1, wherein said deletion
30 comprises a deletion in the polymerase region.

20. The recombinant hybrid virus of Claim 15, wherein said deletion in said polymerase region comprises a deletion at about nucleotides

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7274 to 7881 of the adenovirus serotype 5 genome or a corresponding region of the genome of an adenovirus of another serotype.

21. The recombinant hybrid virus of Claim 1, wherein said heterologous nucleic acid sequence is operatively associated with an expression control sequence.

22. The recombinant hybrid virus of Claim 21, wherein said expression control sequence comprises a promoter.

23. The recombinant hybrid virus of Claim 22, wherein said promoter is selected from the group consisting of a liver-specific, muscle-specific, brain-specific, and glucose-responsive promoter.

24. The recombinant hybrid virus of Claim 22, wherein said promoter is an inducible promoter.

25. The recombinant hybrid virus of Claim 22, wherein said promoter is selected from the group consisting of the CMV promoter, albumin promoter, EF1- α promoter, PyK promoter, MFG promoter, and Rous sarcoma virus promoter.

26. The recombinant hybrid virus of Claim 1, wherein said heterologous nucleic acid sequence encodes a polypeptide.

27. The recombinant hybrid virus of Claim 26, wherein said polypeptide is selected from the group consisting of a therapeutic polypeptide, an immunogenic polypeptide, and a reporter polypeptide.

28. The recombinant hybrid virus of Claim 27, wherein said polypeptide is associated with a lysosomal storage disease.

29. The recombinant hybrid virus of Claim 28, wherein said polypeptide is selected from the group consisting of β -galactosidase, β -hexosaminidase A, β -hexosaminidase B, GM₂ activator protein, glucocerebrosidase, arylsulfatase A, galactosylceramidase, acid sphingomyelinase, acid ceramidase, acid lipase, α -L-iduronidase, iduronate sulfatase, heparan N-sulfatase, α -N-acetylglucosaminidase acetyl-CoA, glucosaminide acetyltransferase, N-acetylglucosamine-6-sulfatase, arylsulfatase B, β -glucuronidase, α -mannosidase, β -mannosidase, α -L-fucosidase, N-aspartyl- β -glucosaminidase, α -neuraminidase, lysosomal

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protective protein, α -N-acetyl-galactosaminidase, N-acetylglucosamine-1-phosphotransferase, cystine transport protein, sialic acid transport protein, the CLN3 gene product, palmitoyl-protein thioesterase, saposin A, saposin B, saposin C, and saposin D.

5 30. The recombinant hybrid virus of Claim 26, wherein said polypeptide is associated with a glycogen storage disease.

31. The recombinant hybrid virus of Claim 30, wherein said polypeptide is selected from the group consisting of glucose 6-phosphatase, lysosomal acid α glucosidase, glycogen debranching enzyme, branching
10 enzyme, muscle phosphorylase, liver phosphorylase, phosphorylase kinase, muscle phosphofructokinase, glycogen synthase, phosphoglucoisomerase, muscle phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase.

32. The recombinant hybrid virus of Claim 31, wherein said
15 polypeptide is a lysosomal acid α -glucosidase.

33. The recombinant hybrid virus of Claim 32, wherein said polypeptide is a human lysosomal acid α -glucosidase.

34. The recombinant hybrid virus of Claim 1, wherein said heterologous nucleic acid sequence encodes an antisense nucleic acid
20 sequence.

35. A hybrid virus particle comprising the recombinant hybrid virus of any of Claims 1 to 34 encapsidated within an adenovirus capsid.

36. A cell comprising the recombinant hybrid virus of Claims 1 to 34 or the hybrid virus particle of Claim 35.

25 37. A method of producing a recombinant adeno-associated virus (AAV) particle, comprising providing to a cell:

- (a) a recombinant hybrid virus according to any of Claims 1 to 34 or a hybrid virus particle according to Claim 35;
- (b) AAV sequences sufficient for replication and packaging of the
30 AAV vector genome; and
- (c) AAV sequences sufficient to produce a functional AAV capsid, wherein (a), (b) and (c) are provided to the cell under

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conditions sufficient for replication of the AAV vector genome and packaging thereof in the AAV capsid such that AAV particles comprising the AAV vector genome encapsidated within the AAV capsid are produced in the cell.

5 38. The method of Claim 37, further comprising the step of collecting the recombinant AAV particle.

 39. The method of Claim 37, further comprising providing to the cell the adenovirus helper functions for AAV replication and packaging.

 40. The method of Claim 39, wherein adenovirus E1a, E2a,
10 E4orf6, and VA RNA helper sequences are provided.

 41. The method of Claim 37, wherein the cell is selected from the group consisting of a HeLa cell, a 293 cell, a muscle cell, and a liver cell.

 42. The method of Claim 37, wherein essentially no adenovirus particles are produced.

15 43. The method of Claim 37, wherein the yield of recombinant AAV particles is at least 5-fold greater than in the presence of the adenovirus polymerase and/or preterminal proteins.

 44. The method of Claim 37, wherein sequences encoding an AAV Rep protein and/or sequences encoding the AAV capsid protein are stably
20 expressed by the cell.

 45. The method of Claim 37, wherein sequences encoding an AAV Rep protein and/or sequences encoding the AAV capsid protein are provided by a vector other than the recombinant hybrid virus.

 46. The method of Claim 45, wherein the vector is selected from
25 the group consisting of a plasmid, an adenovirus, an Epstein Barr virus, and a herpesvirus vector.

 47. The method of Claim 37, wherein the AAV inverted terminal repeats and the AAV capsid are derived from different AAV serotypes.

 48. The method of Claim 37, wherein the AAV capsid is an AAV-6
30 capsid.

 49. The method of Claim 37 or Claim 48, wherein the AAV inverted terminal repeats are AAV-2 inverted terminal repeats.

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50. A method of producing a recombinant adeno-associated virus (AAV) particle, comprising providing to a cell a hybrid virus particle according to Claim 35, said recombinant hybrid virus particle expressing the adenovirus helper functions for AAV replication and packaging; wherein the
5 cell (i) expresses AAV *rep* sequences sufficient for replication and packaging of the AAV vector genome, (ii) expresses AAV *cap* sequences sufficient to produce a functional AAV capsid, and (iii) does not express sequences sufficient to produce a functional adenovirus E1a protein; and further wherein the hybrid virus particle is provided under conditions sufficient for
10 replication of the AAV vector genome and packaging thereof in the AAV capsid such that AAV particles comprising the AAV vector genome encapsidated within the AAV capsid are produced in the cell.

51. A method of producing a recombinant adeno-associated virus (AAV) particle, comprising providing to a cell a hybrid virus particle according
15 to Claim 35, the hybrid virus particle expressing:

- (i) adenovirus helper functions for AAV replication and packaging except the hybrid virus particle does not express a functional adenovirus E1a gene product,
- (ii) AAV *rep* sequences sufficient for replication and
20 packaging of the AAV vector genome, and
- (iii) AAV *cap* sequences sufficient to produce a functional AAV capsid,

wherein the cell expresses functional adenovirus E1a gene products; and further wherein the hybrid virus particle is provided to the cell under
25 conditions sufficient for replication of the AAV vector genome and packaging thereof in the AAV capsid such that AAV particles comprising the AAV vector genome encapsidated within the AAV capsid are produced in the cell.

52. A method of producing a recombinant adeno-associated virus (AAV) particle, comprising providing to a cell:

- 30 (a) a hybrid virus particle according to Claim 35, the hybrid virus particle expressing adenovirus helper functions for AAV

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replication and packaging except the hybrid virus particle does not express a functional adenovirus E1a gene product,

- 5 (b) a separate vector comprising inducible AAV *rep* sequences sufficient for replication and packaging of the AAV vector genome, and AAV *cap* sequences sufficient to produce a functional AAV capsid,

wherein the cell expresses a functional adenovirus E1a gene product; and further wherein (a) and (b) are provided to the cell under conditions sufficient for replication of the AAV vector genome and packaging thereof in the AAV capsid such that AAV particles comprising the AAV vector genome
10 encapsidated within the AAV capsid are produced in the cell.

53. A method of producing a recombinant adeno-associated virus (AAV) particle, comprising providing to a cell:

- 15 (a) a hybrid virus particle according to Claim 35, the hybrid virus particle expressing adenovirus helper functions for AAV replication and packaging,
- (b) a separate vector comprising AAV *rep* sequences sufficient for replication and packaging of the AAV vector genome, and AAV *cap* sequences sufficient to produce a functional AAV capsid,

20 wherein the cell does not express a functional adenovirus E1a gene product; and further wherein (a) and (b) are provided to the cell under conditions sufficient for replication of the AAV vector genome and packaging thereof in the AAV capsid such that AAV particles comprising the AAV vector genome encapsidated within the AAV capsid are produced in the cell.

25 54. The method of Claim 52 or Claim 53, wherein the separate vector is a plasmid vector.

55. The method of Claim 52 or Claim 53, wherein the separate vector is an adenovirus vector.

30 56. A method of introducing a nucleic acid into a cell, comprising contacting a cell with the recombinant hybrid virus of any of Claims 1 to 34 or the hybrid virus particle of Claim 35 under conditions sufficient for entry of the recombinant virus particle into the cell.

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57. The method of Claim 56, wherein the cell is selected from the group consisting of a neuron, a brain cell, a retinal cell, an epithelial cell, a cardiac muscle cell, a smooth muscle cell, a skeletal muscle cell, a diaphragm muscle cell, a pancreatic cell, a liver cell, a fibroblast, an
5 endothelial cell, a germ cell, a lung cell, a prostate cell, a stem cell, a progenitor cell, and a cancer cell.

58. The method of Claim 56, wherein the cell is a mammalian cell.

59. A method of administering a nucleotide sequence to a subject, comprising administering to a subject the recombinant hybrid virus of any of
10 Claims 1 to 34 or the hybrid virus particle of Claim 35 in a pharmaceutically acceptable carrier.

60. The method of Claim 59, wherein the subject is selected from the group consisting of an avian subject and a mammalian subject.

61. The method of Claim 60, wherein the subject is a mammalian
15 subject.

62. The method of Claim 61, wherein the subject is a human subject.

63. The method of Claim 59 or Claim 62, wherein the subject has lysosomal acid α -glucosidase deficiency.

20 64. The method of Claim 59, wherein the recombinant hybrid virus or hybrid virus particle is administered by a route selected from the group consisting of oral, rectal, transmucosal, transdermal, inhalation, intravenous, subcutaneous, intradermal, intramuscular, and intraarticular administration.

65. The method of Claim 59, wherein the recombinant hybrid virus
25 or hybrid virus particle is administered to the liver.

66. The method of Claim 65, wherein the recombinant hybrid virus or hybrid virus particle is delivered to the liver by a method selected from the group consisting of intravenous administration, intraportal administration, intrabiliary administration, intra-arterial administration, and direct injection
30 into the liver parenchyma.

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67. The method of Claim 56 or 59, further comprising introducing an AAV Rep 68/78 protein or sequences encoding an AAV Rep 68/78 protein into the cell.
68. A vector comprising:
- 5 (a) an AAV genome comprising AAV inverted terminal repeats;
- (b) an AAV capsid comprising capsid proteins; and
- (c) a nucleic acid encoding a lysosomal acid alpha-glycosidase polypeptide (GAA).
- 10 69. The vector of claim 68, wherein the AAV genome comprises nucleic acids derived from an AAV1 genome, an AAV2 genome, an AAV3 genome, an AAV4 genome, an AAV5 genome, an AAV6 genome, or combinations thereof.
70. The vector of claim 69, wherein the AAV genome comprises
- 15 nucleic acids derived from an AAV2 genome.
71. The vector of claim 68, wherein the AAV inverted terminal repeats are selected from the group consisting of AAV1 inverted terminal repeats, AAV2 inverted terminal repeats, AAV3 inverted terminal repeats, AAV4 inverted terminal repeats, AAV5 inverted terminal repeats, and AAV6
- 20 terminal repeats.
72. The vector of claim 71, wherein the AAV inverted terminal repeats comprise AAV2 inverted terminal repeats.
73. The vector of claim 68, wherein the AAV capsid proteins comprise capsid proteins selected from the group consisting of AAV1 capsid
- 25 proteins, AAV2 capsid proteins, AAV3 capsid proteins, AAV4 capsid proteins, AAV5 capsid proteins, AAV6 capsid proteins, and combinations thereof.
74. The vector of claim 68, wherein the vector comprises a pseudotyped vector.
- 30 75. The vector of claim 74, wherein the pseudotyped vector comprises:

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- (a) an AAV genome comprising AAV2 inverted terminal repeats;
- (b) an AAV capsid comprising AAV6 capsid proteins; and
- (c) a nucleic acid encoding a lysosomal acid alpha-glycosidase polypeptide (GAA).

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76. The vector of claim 68, wherein the lysosomal acid alpha-glycosidase polypeptide (GAA) comprises a human lysosomal acid alpha-glycosidase polypeptide (hGAA).

77. A composition comprising AAV6 particles and a pharmaceutically acceptable vehicle, wherein the AAV6 particles comprise about 100 AAV6 particles per cell to about 10,000 AAV6 particles per cell upon administration of the composition to a cell.

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78. The composition of claim 77, wherein the AAV6 particles each comprise:

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- (a) an AAV genome comprising AAV inverted terminal repeats; and
- (b) an AAV6 capsid comprising one or more AAV6 capsid proteins.

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79. The composition of claim 78, wherein the AAV genome comprises nucleic acids derived from an AAV1 genome, an AAV2 genome, an AAV3 genome, an AAV4 genome, an AAV5 genome, an AAV6 genome, or combinations thereof.

80. The composition of claim 79, wherein the AAV genome comprises nucleic acids derived from an AAV2 genome.

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81. The composition of claim 78, wherein the AAV inverted terminal repeats are selected from the group consisting of AAV1 inverted terminal repeats, AAV2 inverted terminal repeats, AAV3 inverted terminal repeats, AAV4 inverted terminal repeats, AAV5 inverted terminal repeats, and AAV6 terminal repeats.

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82. The composition of claim 81, wherein the AAV inverted terminal repeats comprise AAV2 inverted terminal repeats.

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83. The composition of claim 78, wherein the AAV6 capsid further comprises one or more capsid proteins selected from the group consisting of AAV1 capsid proteins, AAV2 capsid proteins, AAV3 capsid proteins, AAV4 capsid proteins, AAV5 capsid proteins, and combinations thereof.

5 84. The composition of claim 78, wherein the AAV6 particle comprises a pseudotyped AAV6 particle.

85. The composition of claim 84, wherein the pseudotyped AAV6 particle comprises:

- 10 (a) an AAV genome comprising AAV2 inverted terminal repeats; and
(b) an AAV6 capsid comprising AAV6 capsid proteins.

86. The composition of claim 77, further comprising a nucleic acid encoding a therapeutic polypeptide, a therapeutic nucleic acid, or a combination thereof.

15 87. The composition of claim 86, wherein the therapeutic polypeptide comprises a polypeptide selected from the group consisting of a dystrophin polypeptide, a dystrophin-associated polypeptide, a sarcoglycan polypeptide, a glycogen phosphorylase polypeptide, and a lysosomal alpha-glycosidase (GAA) polypeptide.

20 88. The composition of claim 87, where the therapeutic polypeptide comprises a lysosomal alpha-glycosidase (GAA) polypeptide.

89. The composition of claim 88, wherein the lysosomal alpha-glycosidase (GAA) polypeptide comprises a human lysosomal alpha-glycosidase (hGAA) polypeptide.

25 90. The composition of claim 77, further comprising a detectable label.

91. A method for delivering a nucleic acid to a muscle cell in a subject, the method comprising administering to a muscle of a subject a vector comprising:

- 30 (a) the nucleic acid;

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- (b) an AAV genome comprising AAV inverted terminal repeats; and
- (c) an AAV6 capsid comprising one or more AAV6 capsid proteins,

5 whereby delivery of the nucleic acid to the muscle cell is accomplished.

92. The method of claim 91, wherein the administering comprises intramuscular injection.

93. The method of claim 91, wherein the muscle is selected from the group consisting of cardiac muscle, smooth muscle, skeletal muscle, and
10 diaphragm muscle.

94. The method of claim 91, wherein the subject comprises a mammal.

95. The method of claim 94, wherein the mammal comprises a human.

15 96. The method of claim 91, wherein the AAV genome comprises nucleic acids derived from an AAV1 genome, an AAV2 genome, an AAV3 genome, an AAV4 genome, an AAV5 genome, an AAV6 genome, and combinations thereof.

97. The method of claim 96, wherein the AAV genome comprises
20 nucleic acids derived from an AAV2 genome.

98. The method of claim 91, wherein the AAV inverted terminal repeats are selected from the group consisting of AAV1 inverted terminal repeats, AAV2 inverted terminal repeats, AAV3 inverted terminal repeats, AAV4 inverted terminal repeats, AAV5 inverted terminal repeats, and AAV6
25 terminal repeats.

99. The method of claim 91, wherein the AAV inverted terminal repeats comprise AAV2 inverted terminal repeats.

100. The method of claim 91, wherein the AAV6 capsid further comprises one or more AAV capsid proteins selected from the group
30 consisting of AAV1 capsid proteins, AAV2 capsid proteins, AAV3 capsid

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proteins, AAV4 capsid proteins, AAV5 capsid proteins, and combinations thereof.

101. The method of claim 91, wherein the AAV6 vector comprises an AAV6 pseudotyped vector.

5 102. The method of claim 101, wherein the pseudotyped vector comprises:

(a) an AAV genome comprising AAV2 inverted terminal repeats; and

10 (b) an AAV6 capsid comprising one or more AAV6 capsid proteins.

103. The method of claim 91, wherein the vector further comprises a detectable label.

104. The method of claim 103, further comprising detecting the detectable label.

15 105. The method of claim 91, wherein the vector further comprises a nucleic acid encoding a therapeutic polypeptide, a therapeutic nucleic acid, or a combination thereof.

20 106. The method of claim 105, wherein the therapeutic polypeptide comprises a polypeptide selected from the group consisting of a dystrophin polypeptide, a dystrophin-associated polypeptide, a sarcoglycan polypeptide, a glycogen phosphorylase polypeptide, and a lysosomal alpha-glycosidase (GAA) polypeptide.

107. The method of claim 106, wherein the therapeutic polypeptide comprises a lysosomal alpha-glycosidase (GAA) polypeptide.

25 108. The method of claim 107, wherein the lysosomal alpha-glycosidase (GAA) polypeptide comprises a human lysosomal alpha-glycosidase (hGAA) polypeptide.

30 109. A method of administering a nucleotide sequence encoding a lysosomal acid alpha-glycosidase (GAA) polypeptide to a subject, the method comprising administering to a subject an AAV vector comprising:

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- (a) an AAV genome comprising AAV inverted terminal repeats;
- (b) an AAV capsid comprising capsid proteins; and
- (c) a nucleic acid encoding a lysosomal acid alpha-glycosidase (GAA) polypeptide.

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110. The method of claim 109, wherein the administering comprises transmucosal, transdermal, inhalation, intravascular, subcutaneous, intradermal, intramuscular, and intratumoral administration.

111. The method of claim 109, wherein the subject comprises a mammal.

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112. The method of claim 111, wherein the mammal comprises a human.

113. The method of claim 109, wherein the AAV genome comprises nucleic acids derived from an AAV1 genome, an AAV2 genome, an AAV3 genome, an AAV4 genome, an AAV5 genome, an AAV6 genome, and combinations thereof.

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114. The method of claim 113, wherein the AAV genome comprises nucleic acids derived from an AAV2 genome.

115. The method of claim 109, wherein the AAV inverted terminal repeats are selected from the group consisting of AAV1 inverted terminal repeats, AAV2 inverted terminal repeats, AAV3 inverted terminal repeats, AAV4 inverted terminal repeats, AAV5 inverted terminal repeats, and AAV6 terminal repeats.

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116. The method of claim 115, wherein the AAV inverted terminal repeats comprise AAV2 inverted terminal repeats.

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117. The method of claim 109, wherein the capsid proteins comprise proteins selected from the group consisting of AAV1 capsid proteins, AAV2 capsid proteins, AAV3 capsid proteins, AAV4 capsid proteins, AAV5 capsid proteins, AAV6 capsid proteins, and combinations thereof.

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118. The method of claim 109, wherein the AAV vector comprises an AAV pseudotyped vector.

119. The method of claim 118, wherein the pseudotyped vector comprises:

- 5 (a) an AAV genome comprising AAV2 inverted terminal repeats;
- (b) an AAV6 capsid comprising one or more AAV6 capsid proteins; and
- 10 (c) a nucleic acid encoding a lysosomal acid alpha-glycosidase (GAA) polypeptide.

120. The method of claim 109, wherein the lysosomal acid alpha-glycosidase (GAA) polypeptide comprises a human lysosomal acid alpha-glycosidase (hGAA) polypeptide.

121. The method of claim 109, wherein the vector further comprises
15 a detectable label.

122. The method of claim 121, further comprising detecting the detectable label.

123. A method of administering a nucleotide sequence to a subject comprising a plurality of cells in need thereof, the method comprising
20 administering to a subject a composition comprising AAV6 particles comprising the nucleotide sequence and a pharmaceutically acceptably vehicle, whereby the plurality of cells comprise about 100 AAV6 particles per cell to about 10,000 AAV6 particles per cell.

124. The method of claim 123, wherein the administering comprises
25 transmucosal, transdermal, inhalation, intravascular, subcutaneous, intradermal, intramuscular, and intratumoral administration.

125. The method of claim 123, wherein the subject comprises a mammal.

126. The method of claim 125, wherein the mammal comprises a
30 human.

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127. The method of claim 123, wherein the AAV6 particles each comprise:

- (a) an AAV genome comprising AAV inverted terminal repeats; and
- 5 (b) an AAV6 capsid comprising one or more AAV6 capsid proteins.

128. The method of claim 127, wherein the AAV genome comprises nucleic acids derived from an AAV1 genome, an AAV2 genome, an AAV3 genome, an AAV4 genome, an AAV5 genome, an AAV6 genome, or
10 combinations thereof.

129. The method of claim 128, wherein the AAV genome comprises nucleic acids derived from an AAV2 genome.

130. The method of claim 127, wherein the AAV inverted terminal repeats are selected from the group consisting of AAV1 inverted terminal repeats, AAV2 inverted terminal repeats, AAV3 inverted terminal repeats,
15 AAV4 inverted terminal repeats, AAV5 inverted terminal repeats, and AAV6 terminal repeats.

131. The method of claim 130, wherein the AAV inverted terminal repeats comprise AAV2 inverted terminal repeats.

20 132. The method of claim 127, wherein the AAV6 capsid further comprises one or more capsid proteins selected from the group consisting of AAV1 capsid proteins, AAV2 capsid proteins, AAV3 capsid proteins, AAV4 capsid proteins, AAV5 capsid proteins, and combinations thereof.

25 133. The method of claim 123, wherein the AAV6 particles each comprise a pseudotyped AAV6 particle.

134. The method of claim 133, wherein the pseudotyped AAV6 particle comprises:

- (a) an AAV genome comprising AAV2 inverted terminal repeats; and
- 30 (b) an AAV6 capsid comprising AAV6 capsid proteins.

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135. The method of claim 123, wherein the composition further comprises a nucleic acid encoding a therapeutic polypeptide, a therapeutic nucleic acid, or a combination thereof.

5 136. The method of claim 135, wherein the therapeutic polypeptide comprises a polypeptide selected from the group consisting of a dystrophin polypeptide, a dystrophin-associated polypeptide, a sarcoglycan polypeptide, a glycogen phosphorylase polypeptide, and a lysosomal alpha-glycosidase (GAA) polypeptide.

10 137. The method of claim 136, where the therapeutic polypeptide comprises a lysosomal alpha-glycosidase (GAA) polypeptide.

138. The method of claim 137, wherein the lysosomal alpha-glycosidase (GAA) polypeptide comprises a human lysosomal alpha-glycosidase (hGAA) polypeptide.

15 139. The method of claim 123, wherein the composition further comprises a detectable label.

140. The method of claim 139, further comprising detecting the detectable label.

141. The method of any one of claims 106-122 and 136-138, wherein the subject has lysosomal acid α -glucosidase deficiency.

20 142. A composition comprising about 7,000 AAV6 particles per packaging cell.